Lasers in Surgery and Medicine 18:39–45 (1996)

Intraoperative Photodynamic Therapy With m-Tetrahydroxyphenylchlorin for Chest Malignancies

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Background and Objective: **Since there is no satisfactory treatment modality for diffuse malignant mesothelioma of the chest, we assessed surgical tumor resection followed by intraoperative photodynamic therapy with mTHPC in a phase I study.**
Study Design/Materials and Methods: **Since 1990, eight patients have undergone intraoperative photodynamic therapy with m-tetrahydroxyphenylchlorin (mTHPC-PDT) following thoracotomy and surgical tumor resection.**
Results: **mTHPC-PDT-mediated tumor necrosis was characterized by tumor infarction due to tumor vessel necrosis and thrombosis, and its extent depended on drug-light conditions; 650 nm light delivered at 0.1 W/cm^2 for 10 J/cm^2 48 h after iv administration of 0.3 mg mTHPC/kg resulted in a 10-mm-deep complete tumor necrosis. Skin photosensitivity was related to the drug dose applied and occurred up to 17 days after iv administration of 0.3 mg mTHPC/kg, mTHPC-PDT of brachial plexus infiltrated by mesothelioma resulted in pain relief without deterioration of nerve function.**
Conclusion: **Tumor resection and intraoperative mTHPC-PDT of the chest cavity is feasible under clinical conditions and offers local tumor control of sites involved. However, distant tumor spread was not prevented by this combined treatment modality and optimization of mTHPC-PDT is warranted for further intraoperative application.**

Key words: malignant histiocytoma, malignant mesothelioma, m-tetrahydroxyphenylchlorin, photochemotherapy, surgical tumor resection

INTRODUCTION

Photodynamic therapy (PDT) is an attractive antitumor therapy with selective tumor destruction while sparing unaffected tissues. It might be a useful adjunct to surgical tumor resection in situations without cleavage plane between the tumor and the underlying normal structures and for the treatment of tumors with a high tendency for local recurrence. Several reports have documented the feasibility of intraoperative PDT following surgical tumor resection under clinical conditions [1–5]. However, a high tumor selectivity and efficacy for PDT are required for this purpose to achieve tumor control without injuring underlying vital structures. Since HPD is not an

Received for publication September 29, 1994.

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TABLE 1. Intraoperative mTHPC-PDT Following Surgical Tumor Resection for Chest Malignancies

	Histology[a]	Surgery[b]	mTHPC (mg/kg)	Time interval (d)	Light dose (J/cm^2)	
					Diaphragm	Cavity
1	M	PP	0.3	2	10	5
2	M	PP	0.3	2	10	5
3	M	D	0.3	2	10	5
4	M	PP	0.3	2	10	5
5	M	DL	0.3	3	10	5
6	M	PP	0.3	3	10	5
7[c]	M	D	0.3	3	—	10
8[d]	H	DL	0.3	3	10	—

[a]M = mesothelioma, H = histiocytoma.
[b]PP = pleuropneumonectomy, D = decortication, DL = decortication and lobectomy.
[c]PDT of invaded brachial plexus only due to distant tumor spread.
[d]No PDT of remainder of thoracic cavity due to dense adhesions from previous surgery.

ideal sensitizer in this respect, new compounds are currently being developed. Among them, meta-tetrahydroxyphenylchlorin (mTHPC) has shown excellent antitumor activity and tissue selectivity in rodents without causing significant toxicity [6]. Since 1990 we have evaluated PDT using mTHPC as sensitizer on selected patients with chest malignancies, and the results are summarized in this report.

MATERIALS AND METHODS

Seven patients with malignant mesothelioma and one with recurrent malignant fibrous histiocytoma of the chest cavity underwent thoracotomy and surgical tumor resection followed by intraoperative mTHPC-PDT of the chest cavity involved. PDT was performed as surface irradiance with nonthermal light doses on all nine patients. All patients understood the experimental design of this treatment and consent was obtained from the local Human Investigations Committee of our institution (4.6.1990).

Preliminary PDT was performed on the first two patients of this series with mesothelioma at different drug–light conditions and drug–light intervals [5]. mTHPC (Scotia Pharmaceuticals, Guildford, UK) was dissolved in 20% ethanol, 30% polyethylene glycol 400, and 50% H_2O and administered over 15 min iv through a bacterial filter under sterile conditions within 60 minutes of preparation. Argon-pumped dye laser light of 650 nm (Coherent Innova 200 and Dye CR 599, GMP SA, Lausanne, Switzerland) was delivered through a sterilized optical fibre on tumor areas of 3 cm in diameter. The power at the end of the optical fibre was measured with a power meter, allowing for a power density of 0.1 Watt/cm^2 on the treated surfaces (nonthermal surface irradiation). Biopsies were taken 5 days after light delivery and compared to untreated tumor. Among the various drug–light conditions tested, 10 J/cm^2 and 0.1 W/cm^2 delivered 48 h after administration of 0.3 mg mTHPC/kg gave the best results with a 10 mm deep tumor necrosis.

From the results obtained, intraoperative mTHPC-PDT following tumor resection was performed on eight patients (Table 1). All patients received 0.3 mg mTHPC/kg i.v. The drug–light interval was 48 h for the first four patients. Since the results emerging from our experimental work on nude mice bearing human mesothelioma xenografts indicated that normal tissue was less affected with time intervals ranging from 3–5 days [7], a drug–light interval of 72 h was applied to the other four patients of this series. After 48 h and 72 h, respectively, the chest was opened by standard thoracotomy and the surgical tumor resection was performed according to the type and extent of the tumor. Four patients underwent extrapleural pneumonectomy, two pleurectomy with lobectomy, and two decortication. The diaphragm was debulked yet preserved in order to maintain this natural barrier against further tumor spread.

After completion of the surgical procedure, argon-pumped dye laser light of 650 nm wavelength was delivered through the open chest wound to sites involved in overlapping spots using a sterilized quartz optical fibre without using a lens. Six patients received 10 J/cm^2 to the diaphragm and costophrenic sulcus and 5 J/cm^2 to the remainder of the thoracic cavity. The tumor was predominantly localized on the diaphragm and the lower part of the thoracic cavity, whereas

the upper part of the cavity was less involved. Therefore only 5 J/cm^2 were applied to this part in order to avoid harm to underlying structures and to reduce the treatment time. The mediastinum was shielded by a moist towel if parts of the pericardium had to be removed (5 patients). One patient with recurrent histiocytoma localized in the costodiaphragmatic sulcus and lower lobe did not receive light to the upper thoracic cavity and to the upper lobe since no tumor was visualized on the CT-scan in this area and because of dense adhesions related to prior operations. One patient suffered from intractable pain due to tumor infiltration of the brachial plexus. Peritoneal tumor spread precluded major resection. Previous surgical plexus release by a supraclavicular approach did not help to reduce the pain and mTHPC-PDT was performed to the plexus involved. The plexus was exposed through thoracotomy and local decortication of the pleural dome, and 10 J/cm^2, 0.1 W/cm^2 were delivered in overlapping spots of 2 cm in diameter by use of a lens.

mTHPC concentrations were assessed in blood, tissue (tumor, bronchus, pulmonary artery, lung, skin, muscle), and urine samples by use of high performance liquid chromatography (HPLC) [9,10]. The specimens were frozen at −20°C and 200 mg of the tissues were homogenized in 2 ml of the homogenizing medium (8 parts methanol-DMSO 4:1 v/v containing the internal standard paratetrahydroxyphenylchlorin and 1 part water) in a Dounce homogenizer. The mixture was transferred into a clean tube and centrifuged at 2,600 *g* for 10 min. 400 μl of the supernatant was mixed with 200 μl of water and 200 μl of the solution was injected. The column consisted of hypersil-ODS (5 μm) and the mobile phase of acetonitrile—0.1% TFA (77:23 v/v). The flow rate was 1 ml/min. A linear UVIS-204 detector set at 416 nm and a Perkin-Elmer LS-3 fluorometer set at 406 nm (excitation) and 653 nm (emission) were used.

Patients were cautioned to avoid direct sunlight for about 2 weeks but were encouraged to test skin sensitivity by daily exposure of the hand for a short period of time.

RESULTS

Effect of mTHPC-PDT on Tumor Tissue

These results emerged from the first two patients where preliminary PDT was performed on small areas of mesothelioma for various drug–light conditions [5]. Tumor necrosis was due to tumor infarction, induced by tumor vessel necrosis and thrombosis. A typical watershed phenomenon was observed with a cuff of tumor cells of questionable viability around the thrombosed vessels and frank necrosis of tumor tissue situated far away (Fig. 1b). It was found that a drug dose of 0.3 mg mTHPC/kg and a light dose of 10 J/cm^2 delivered after 48 h resulted in a 10-mm-deep complete tumor necrosis of both, epithelial and biphasic mesothelioma (Fig. 1c).

mTHPC Pharmacokinetics

Plasma concentrations followed a first-order kinetics after i.v. application with a half-life time of 12 h. An average plasma concentration of 14.6 ± 7.6 μg/100ml was measured 48 h after administration of 0.3 mg mTHPC/kg.

No mTHPC or metabolites were identified in urine samples at any time. There was a preferential uptake in tumor tissues as measured in harvested specimens by use of HPLC, with a tumor-skin ratio varying from 3:1 to 14:1, and a tumor-bronchus ratio varying from 4:1 to 6:1 at a drug–light interval of 48 h. The highest tumor/skin ratio was obtained for malignant histiocytoma (14:1). However, caution in the interpretation of mTHPC tissue concentration measurements is indicated, since the drug concentration was 100 times higher in plasma than in tissues 48 h after drug administration. mTHPC tissue concentration measurements might have been biased by blood spillage of the harvested specimens.

Photobleaching

The mTHPC concentration was measured in one patient by use of HPLC in tumor specimens (mesothelioma) before and just after light delivery (10 J/cm^2, 0.1 W/cm^2) 72 h after drug administration (0.3 mg/kg). A 75% decrease of the mTHPC concentration in the tumor specimens was observed after exposure to light. Again, caution in the interpretation is indicated since only one measurement could be obtained.

Skin photosensitivity was strongly related to the drug dose applied. No skin reaction was observed after administration of 0.1 mg mTHPC/kg. However, it occurred up to 2 ½ weeks after i.v. administration of 0.3 mg mTHPC/kg. Here, it was observed after direct and indirect (closed window) exposure to sunlight, but not under normal room light conditions. However, skin necrosis occurred in one patient after exposure to bright light of an operating theatre lamp 24 h after administration of 0.3 mg mTHPC/kg. This lamp emitted the full spectrum with a high percentage of red light.

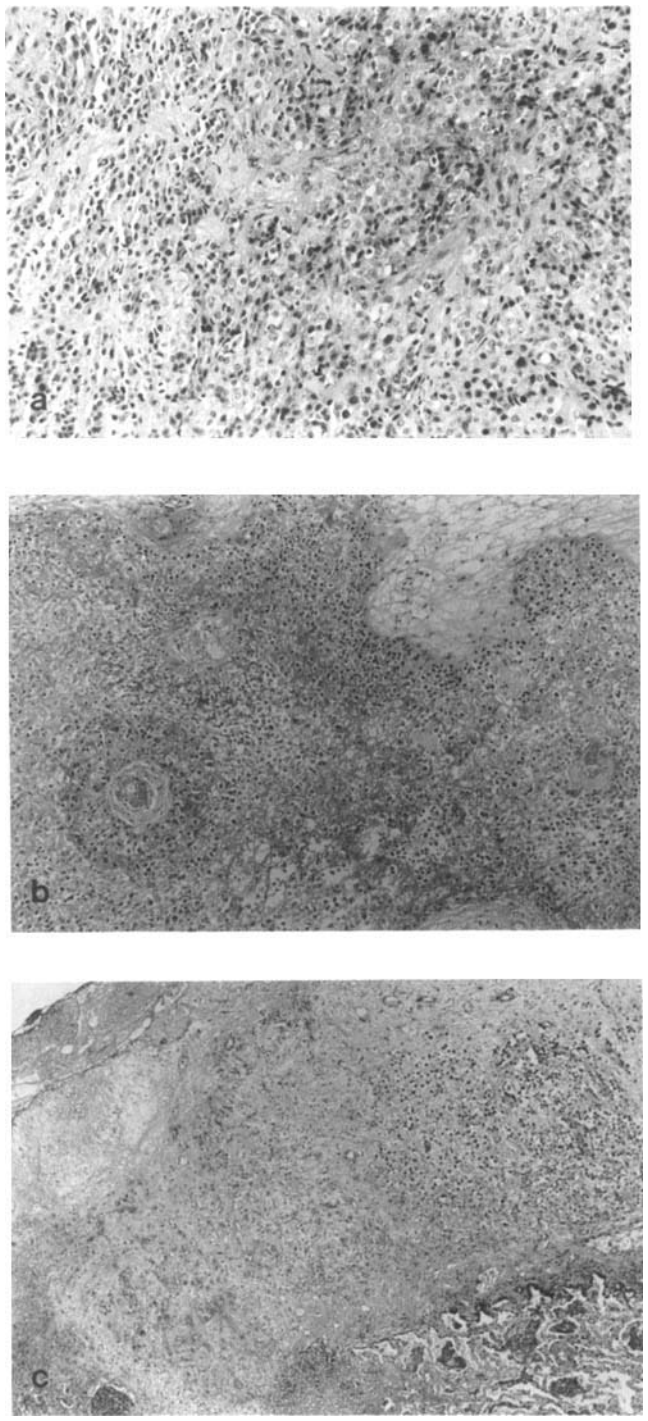

Fig. 1. Photodynamic therapy with mTHPC for malignant mesothelioma: (**a**) untreated tumor (H&E, ×200), (**b**) tumor infarction due to tumor vessel thrombosis at 0.075 mg/kg and 10 J/cm^2 (H&E, ×100), arrow indicates watershed phenomenon with a cuff of tumor cells of questionable viability around the thrombosed vessel and frank tumor necrosis farther away, (**c**) 10 mm deep tumor necrosis after 0.3 mg/kg and 10 J/cm^2 (H&E, ×100), arrows indicate the surface of the tumor as well as that of the underlying lung. Histological assessment 5 days after light delivery.

Postoperative Course

The drug itself was well tolerated apart from the skin phototoxicity. Intraoperative PDT following surgical tumor resection led to additional morbidity beyond that of surgery alone such as loss of appetite, fluid retention, hypoproteinemia, and severe chest pain. One patient developed a sealed colonic perforation on the left flexure, which was discovered 3 weeks after PDT; 10 J/cm^2 was delivered in this patient to the debulked diaphragm overlying the colon. At laparotomy the debulked diaphragm overlying the perforated colon was found intact. The patient was under high-dosed oral steroids, which might also have led to this sealed colonic perforation. However, the pattern of tissue damage of the resected colonic specimen was similar to that observed in tumor tissue after mTHPC-PDT. Temporary diversion colostomy was performed and was reversed 2 months later. One patient succumbed from aspiration-induced pneumonia of the contralateral lung after decortication and intraoperative mTHPC-PDT 6 days after the operation, giving a 30-day mortality of 13% after surgical tumor resection and intraoperative mTHPC-PDT of the chest involved. The autopsy of this patient revealed a 5–10-mm-deep PDT necrosis of the remnant tumor (sarcomatous mesothelioma). Normal underlying structures such as the aorta, subclavian artery, and brachial plexus, and the oesophagus were spared, even in view of a close relationship between the tumor and normal tissues (Fig. 2).

Follow-up after intraoperative PDT following surgical tumor resection revealed no vascular or neural alterations, either on clinical grounds or on CT-scans. One patient developed a small bronchopleural fistula after lobectomy (stapling technique) that did not require reoperation. The patient with plexus infiltration remained pain-free without further neurologic deterioration until death 4 months after the operation due to tumor progression. The sites treated by surgery and PDT remained free of disease during follow-up as judged on repeated CT-scans (Fig. 3), but all patients suffering from mesothelioma developed distant metastases or contralateral disease 4–18 months after the procedure.

DISCUSSION

Diffuse malignant mesothelioma poses a significant problem since there is no standard therapy for this usually fatal disease. All forms of

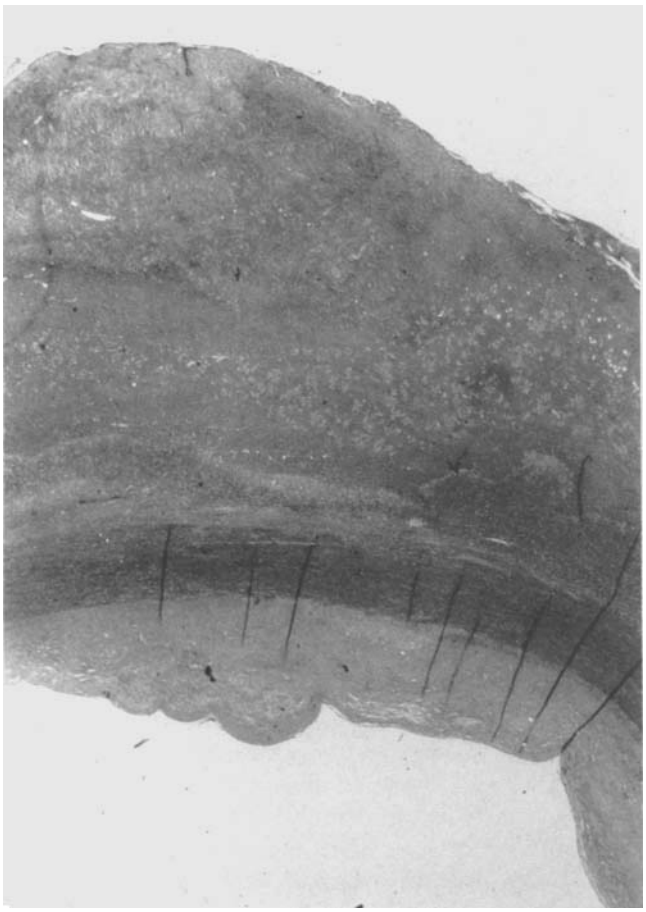

Fig. 2. Autopsy findings after intraoperative mTHPC-PDT of the chest cavity for malignant mesothelioma (sarcomatous type). Destroyed tumor infiltrating the aorta with spared vessel wall. (H&E, ×16), arrow indicates borderline between necrotic tumor and intact vessel wall.

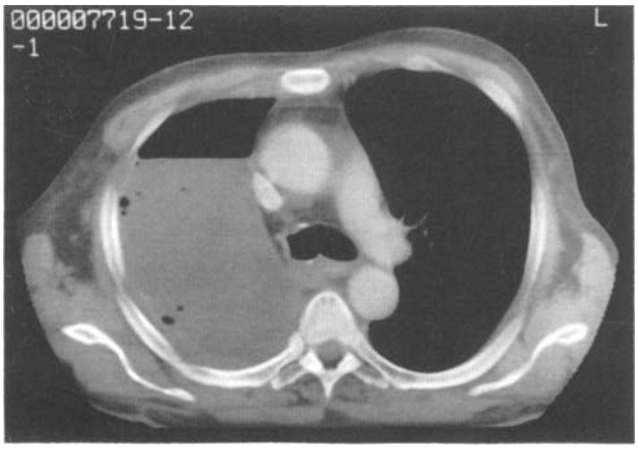

Fig. 3. CT-scan without evidence of gross disease 12 months after extrapleural pneumonectomy and intraoperative mTHPC-PDT for malignant mesothelioma.

treatment have failed to control tumor regrowth and improve survival. Because radiation and chemotherapy are relatively ineffective in mesothelioma [11–13], surgical resection has been considered the mainstay of treatment. However, the only prospective evaluation of surgery in malignant mesothelioma conducted by the Lung Cancer Study Group has failed to show any improvement of survival after surgical tumor resection compared to medical treatments or no treatment at all. Twenty selected patients underwent radical extrapleural pneumonectomy, but this did not result in better survival, and 13 developed local recurrence during follow-up [14]. Five-year survival is exceptional for patients with diffuse malignant mesothelioma, regardless the treatment performed [15].

Therefore, new therapeutic approaches are warranted for this disease. Intraoperative PDT following surgical tumor resection might be an attractive concept, allowing for a selective clean-up of the tumor bed after gross tumor removal with destruction of remnant disease while leaving underlying vital structures intact. Natural barriers against further tumor spread might be preserved, first of all the diaphragm. PDT has been reported to be effective in human malignant mesothelioma xenografts [16]. However, for clinical purposes light must be delivered to the thoracic cavity encompassing large and complex-shape areas bordered by vital structures, which might lead to dreadful complications if injured by unselective PDT. Extrapleural pneumonectomy per se is already a formidable procedure with an operative mortality ranging from 10% to 20% in several series [17,18]. Since 1990 we have assessed PDT in a pilot study on selected patients suffering from malignant mesothelioma. To overcome the well-known drawbacks of Photophrin, new sensitizers are currently being developed [19–21], and we have chosen mTHPC as sensitizer since it seems to be more effective at inducing tumor necrosis than Photophrin [6].

Our results indicated that the drug itself was well tolerated and up to 0.3 mg/kg did not cause side effects other than skin photosensitivity. Skin photosensitivity was dependent upon the drug dose applied. No sensitivity was observed if 0.1 mg mTHPC/kg were administered but it occurred up to 2 ½ weeks after administration of 0.3 mg/kg, and frank necrosis of skin was observed on one patient at this dose. These appear to be accidental

exposures or exposures due to noncompliance and no prospective trial for determining minimal erythemal dose using mTHPC has been performed at date. However, our preliminary results indicate that a lower drug dose (e.g., 0.1 mg/kg) might be used for further clinical application to avoid skin photosensitivity.

mTHPC concentration measured by use of HPLC revealed a first-order kinetics for plasma concentrations with a half-life of 12 h. No mTHPC or metabolites were identified in urine samples, indicating that the drug is eliminated by hepatobiliary secretion. mTHPC tissue concentrations measured by HPLC must be interpreted with caution since the mTHPC concentration was 100 times higher in plasma than in tissues and tissue concentration measurements might have been biased by blood spillage of the specimens that were not washed after harvesting. mTHPC-PDT mediated deep tumor necrosis with low light doses. A 10 mm deep tumor necrosis was obtained with only 10 J/cm^2, which could not be attributed to thermal effects. This extent of necrosis was obtained with the same drug–light conditions for all histological types of mesothelioma (epithelial, biphasic, and sarcomatous). The photosensitizing effect consisted of tumor infarction due to tumor vessel necrosis and thrombosis, indicating that the tumor vessel might be the primary target for mTHPC-PDT [5].

The autopsy findings of the patient who died 6 days after tumor resection and intraoperative PDT revealed that the tumoricidal effect of mTHPC-PDT is not affected by previous surgical tumor debulking. The extensive tumor necrosis bordered by healthy muscle, bronchus, vessels, and nerves with apparent absence of necrosis in this patient demonstrated that mTHPC-PDT offers a high a potential of treatment selectivity. This was further outlined by the successful treatment of a patient with tumor invasion of his brachial plexus by mTHPC-PDT. The patient was referred after unsuccessful surgical plexus release, which did not help to relieve the pain related to tumor invasion of the plexus. However, successful pain relief was obtained by intraoperative PDT of the plexus involved, and no deterioration of nerve function was observed after the procedure. In addition, no vascular alteration was observed in any patient of this small series as judged on clinical grounds and on repeated CT-scans during follow-up.

Although the postoperative mortality in this small series was comparable to that of other reports dealing with conventional surgery [14], the postoperative course of our patients was marked by a significant additional morbidity, beyond that expected from surgery alone. We do not know if the colonic perforation that occurred in one patient must be attributed to intraoperative mTHPC-PDT since the overlying diaphragm was intact and the patient was on steroids. However, the histologic pattern of the resected specimen was similar to that observed in tumor tissue after PDT.

In this small series of patients with recurrent or advanced pleural tumors, no recurrence was observed at sites involved by surgery and PDT during follow-up. However, all patients developed tumor spread to nodes, contralateral chest, and to distant sites, and all patients died from their disease during follow-up. It was believed that patients suffering from malignant mesothelioma succumb from relentless local progression of the disease [23]. Since better local tumor control is now available, it becomes apparent that malignant mesothelioma has a high metastatic potential requiring a combination of local and systemic therapy in order to improve survival.

We found a preferential uptake of mTHPC in malignant fibrous histiocytoma involving the chst cavity and lung. Tumor control was obtained by surgery and PDT, but no conclusion can be drawn from one single patient.

In summary, mTHPC is an effective second-generation sensitizer for photodynamic therapy. Intraoperative mTHPC-PDT is feasible under clinical conditions but is related to additional morbidity if large areas are treated. A perfect tissue selectivity is mandatory for all effective new sensitizers that absorb strongly at longer wavelengths in order to prevent extensive damage to normal structures. Enhanced treatment selectivity of mTHPC-PDT was indeed demonstrated in an experimental setting by modulations of the drug-light conditions [7,8]. However, further efforts need to be done before intraoperative PDT can be proposed as a safe and effective treatment.

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